Positioning the principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis - A EUFOREA-ARIA-EPOS-AIRWAYS ICP statement

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Positioning the principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis – A EUFOREA-ARIA-EPOS-AIRWAYS ICP statement

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Abstract

Precision medicine (PM) is increasingly recognized as the way forward for optimizing patient care. Introduced in the field of oncology, it is now considered of major interest in other medical domains like allergy and chronic airway diseases, which face an urgent need to improve the level of disease control, enhance patient satisfaction and increase effectiveness of preventive interventions. The combination of personalized care, prediction of treatment success, prevention of disease and patient participation in the elaboration of the treatment plan is expected to substantially improve the therapeutic approach for individuals suffering from chronic disabling conditions. Given the emerging data on the impact of patient stratification on treatment outcomes, European and American regulatory bodies support the principles of PM and its potential advantage over current treatment strategies. The aim of the current document was to propose a consensus on the position and gradual implementation of the principles of PM within existing adult treatment algorithms for allergic rhinitis (AR) and chronic rhinosinusitis (CRS). At the time of diagnosis, prediction of success of the initiated treatment and patient participation in the decision of the treatment plan can be implemented. The second-level approach ideally involves strategies to prevent progression of disease, in addition to prediction of success of therapy, and patient participation in the long-term therapeutic strategy. Endotype-driven treatment is part of a personalized approach and should be positioned at the tertiary level of care, given the efforts needed for its implementation and the high cost of molecular diagnosis and biological treatment.

KEYWORDS
allergic rhinitis, integrated care pathway, precision medicine, rhinosinusitis

1 | INTRODUCTION

A new paradigm to advance medical care is precision medicine (PM).[1] The four Ps of PM stand for personalized, predictive, preventive and participatory. PM encourages a convergence of omics, systems medicine, innovative health information technology and consumer-driven health care. Global multidiscipline partnerships and the right balance between research and policy priorities are needed to achieve the audacious goal of PM. Applying the principles of PM at the point of care is one of the major challenges for development of the future healthcare system.

Precision medicine is a medical model aiming at the customization of health care—with medical decisions, practices and/or products tailored to the individual patient.[2] Based on the knowledge of mechanisms of the disease, PM generally combines diagnosis and treatment to select optimal management.[3,4]

The concept of PM is not new. Clinicians have always observed that patients with similar symptoms may have different diseases, with different causes, and that treatment may have different outcomes depending on a multitude of individual external and endogenous factors. The novelty comes from the rapid technological advances, including omics, medical imaging, regenerative medicine, biobanks and registries, along with an increased computational power and innovative health information technology (HIT). This will allow real-time clinical decision support at the point of care with implementation of harmonized care based on quality criteria and patients to be treated and monitored more precisely and effectively to better meet their individual needs.[2] In addition, other providers will play a larger role in routine care for less complex cases and during follow-up.

Precision medicine is rapidly gaining more attention in molecular diagnosis-based treatment of cancer[5] and other diseases. The practical implementation of PM is however more difficult in complex diseases such as multimorbid chronic diseases.[3,6] Nonetheless, one recent example of successful application was reported in cystic fibrosis. In 4% of the patients, the specific intervention based on the molecular mechanism can totally reverse the disorder.[7] In allergic diseases, PM principles have always been used, in particular for patients receiving allergen immunotherapy (AIT).[8] AIT is tailored to the patient's sensitization profile and it has a long-lasting and preventive effect.[9] Despite major advances in understanding allergic diseases, many patients with upper airway diseases are still uncontrolled[10,11] and primary prevention is still unknown. Recently, a PRACTALL report highlighted the need for PM in airway diseases.[12]

Chronic upper airway inflammation can be roughly divided into two major clinical entities, that is rhinitis and rhinosinusitis. The allergic phenotype is the best characterized phenotype of rhinitis from a pathophysiologic point of view.[13] The diagnosis of allergic rhinitis (AR) requires the proof of IgE-mediated hypersensitivity using appropriate skin or blood tests and the implication of the relevant allergen in eliciting the symptoms.[14] Allergic and nonallergic rhinitis often coexist, but the treatment response differs,[15] and many patients only use "over-the-counter" (OTC) medications.[16] Chronic rhinosinusitis (CRS) is classically divided into a phenotype with and without endoscopic or radiologic evidence of nasal polyps (CRSwNP and CRSsNP, respectively).[17]

Both AR and CRS are characterized by inflammation and are divided into the mild, moderate and severe subgroups, and for both, anti-inflammatory medication represents the first-line treatment.[13,17,18] The use of nasal endoscopy and CT imaging may not be sufficient to fully appreciate the individual patients' pathology. Endotyping of CRS on the basis of physiological, functional and pathological characteristics might provide information on the risk of disease progression or recurrence and on the best available treatments, and also helps in identifying innovative therapeutic targets for treatment.[19]

The Allergic Rhinitis and its Impact on Asthma (ARIA) treatment algorithms provide evidence-based guidelines for treatment of AR.[13,20] Multiple treatment options, strategies and approaches can be applied depending on the level of control achieved or aiming for. In AR, AIT is recommended when pharmacotherapy is not successful, or as an alternative to long-term pharmacotherapy. Surgical reduction of the inferior turbinate(s) or correction of a septal deviation might be indicated when nasal obstruction persists as a major symptom in adequately medically treated AR patients. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) treatment algorithms provide evidence-based guidelines for treatment of CRS.[17] Anti-inflammatory medication in combination with saline douching represents the first step of treatment for CRS, with adaptation of the therapeutic regimen dependent on the degree of control.[17] Surgery is considered if prolonged medical treatment fails, but up to 40% of patients remain symptomatic despite sinus surgery.[21]

Medical treatment for any condition aims at controlling the disease including clinically significant symptom reduction with improvement of quality of life and reduction of socio-economic impact of the disorder. In contrast to other diseases like asthma[22] and despite the high prevalence of AR and CRS,[23,24] the concept of control of disease has only recently been introduced in AR[10,25] and CRS.[17] However, this concept is important to define those patients with difficult-to-treat disease, representing a diagnostic and therapeutic challenge and having a large socio-economic burden.[26,27] After defining those patients with uncontrolled disease, factors associated with lack of control can be identified, and better insights can be obtained in global airway disease control.[28] Recently, uncontrolled disease in AR and CRS has been reported to reach 35% and 40% of patients treated in academic referral centres respectively, underscoring the need for novel and better strategies of care for both AR and CRS.[21,29] Nowadays, it is clear that there is a need to optimize treatment and embrace the principles of PM in chronic airways diseases in order to achieve a higher level of control of disease.

This review is an initiative taken by the nonprofit EUFOREA leadership in conjunction with ARIA, EPOS and AIRWAYS ICPs [16,17,30] (European Innovation Partnership on Active and Healthy Ageing, Action Group B3) experts who felt the need to provide a comprehensive overview of the current state of the art on control in upper airway diseases, with a focus on the different factors involved in uncontrolled upper airway inflammation as well as the unmet needs in this domain. In addition, a proposal for gradual implementation of the principles of PM into the adult management algorithms of AR and CRS is made.

2 | GRADUAL IMPLEMENTATION OF THE FOUR PRINCIPLES OF PRECISION MEDICINE IN ALLERGIC RHINITIS

2.1 | First-level management of AR

Allergic Rhinitis is diagnosed based on the combination of a history of two or more nasal symptoms, nasal examination showing inflammatory changes in untreated patients and confirmation of the suspicion of sensitization by skin prick tests or specific IgE tests.

At the time of the first diagnosis of AR in medical or specialist office, a therapeutic plan is elaborated taking into account the major presenting symptoms, the severity and impact of symptoms, comorbidities and availability of treatment (Figure 1).

At present, it seems clear that two key principles of PM can easily be implemented at the time of elaboration of a therapeutic plan (Figure 2):

- *Prediction of success of treatment:* The treatment strategy may be guided using a recent algorithm proposed by worldwide experts.[31] Physicians treating patients with AR should be aware of the different therapeutic strategies for AR and adapt to the patients' profile (MACVIA-ARIA), preferences and needs, taking into account the availability and accessibility to the recommended treatment choice. Up to 50% of patients treated for AR want to be informed about the different treatment options and strategy applied at the time of diagnosis.[32] Therefore, the following information on prediction of success of treatment on nasal, ocular, bronchial and general symptoms should be communicated to AR patients:
    - Information on the expected onset of action and benefit of treatment of different treatment options, both on symptom severity and on general functioning and quality of life
    - Information on the shortcomings, safety and potential adverse events of different treatment options and approaches
    - Information on the impact of treatment of AR on the comorbidities, like asthma, otitis media and eczema

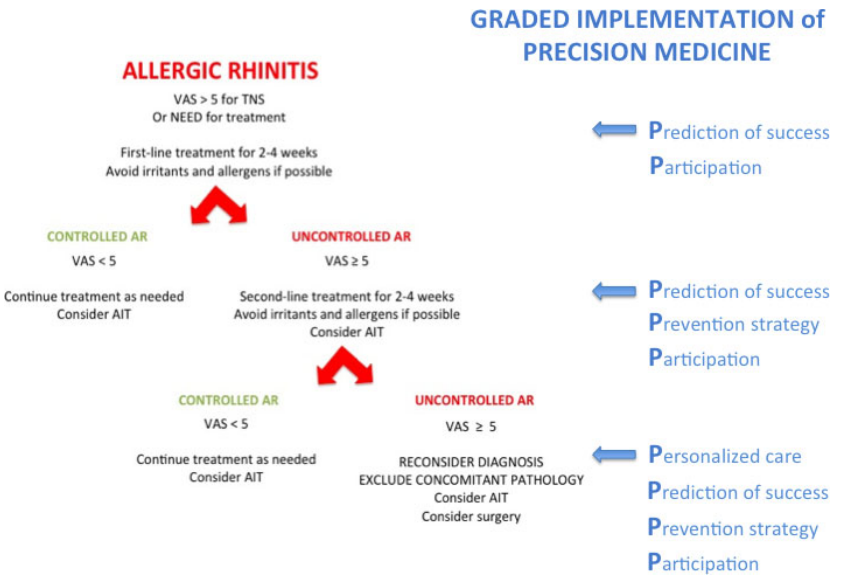

FIGURE 1 Graded implementation of precision medicine in allergic rhinitis (adapted from Hellings et al. [11]). VAS, visual analogue scale; TNS, total nasal symptoms; IT, immunotherapy; AR, allergic rhinitis

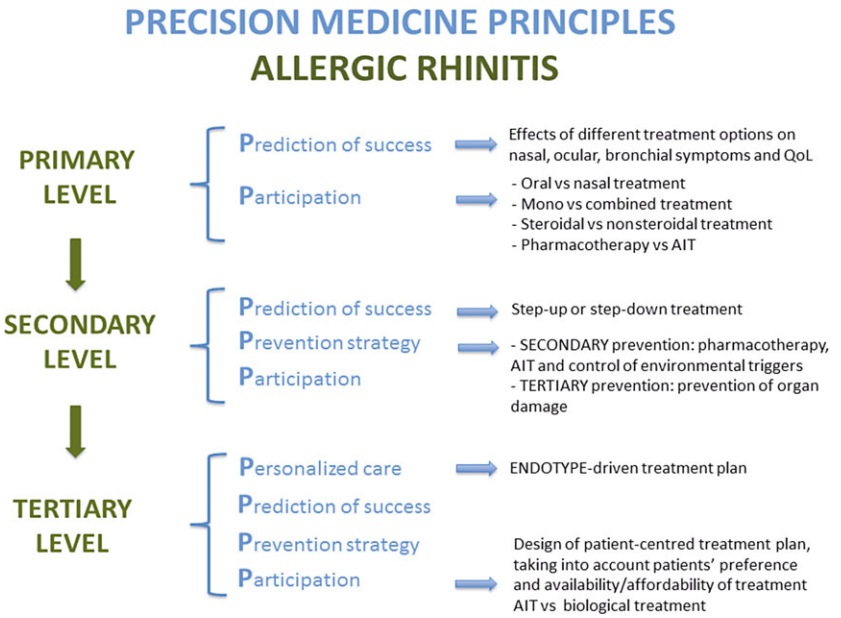

FIGURE 2 Precision medicine implementation in allergic rhinitis. Qol, quality of life; AIT, allergen immunotherapy

- *Participation of the patient*: Given the proven efficacy of several active compounds for AR, the different routes of administration of treatment and the different aims of treatment, patients can be empowered to become an active partner in the elaboration of the following strategic choices for first-line treatment for AR (after receiving and understanding the above info):
  - Choice of oral versus nasal route of administration of effective molecules
  - Choice of combined treatment versus monotherapy
  - Choice of corticosteroidal versus noncorticosteroidal treatment options
  - Choice of pharmacological treatment versus allergen-specific immunotherapy

Patient education is crucial in this process to allow patients to assess and self-monitor symptom severity and control, to properly use medication and to be informed about whom to seek for medical advice.

After having elaborated a treatment strategy with the AR patient, it is recommended to evaluate the degree of symptom control regularly using mobile technology or after a time interval of 2-4 weeks by physician's visits. Symptom control in AR can be evaluated via different means, but a visual analogue scale (VAS) score seems to be a good tool for control evaluation in real clinical life.[29,33,34] Telemonitoring enables convenient evaluation of patients on a regular basis. Clinical Decision Support Systems (CDSS), interactive computer software, is designed to assist health professionals with decision-making tasks, such as determining

treatment strategies of patient using the results of ICPs. MASK (MACVIA-ARIA sentinel network for rhinitis) includes all these features.[31,35,36]

2.2 | Second-level management of AR

Following the initiation of first-line treatment, uncontrolled patients are invited for evaluation of symptom control and fine-tuning of the treatment strategy accordingly. Besides taking into account the achieved level of control by first-line treatment, a treatment strategy is elaborated according to the revised needs and expectations of the patient, the experienced efficacy and/or adverse events of the medication used, the availability of medication and the long-term goal of maintaining or achieving disease control and prevent disease progression.

Therefore, the following three key principles of PM can be implemented during the follow-up consultation for AR (Figure 2):

- *Prediction of success* of any step-down or step-up approach, based on the input from the patient on the expected benefits
- *Participation of the patient* in the management plan
- *Prevention of disease progression* with clear statements on the different approaches for suppression of inflammation vs prevention of disease progression:
  - Secondary prevention aims at preventing the acquisition of new sensitizations and the onset of asthma in those AR patients who have not developed asthma yet. Evidence-based therapeutic interventions for the secondary prevention of asthma fall into three categories:
    - Pharmacological treatment
    - Allergen-specific immunotherapy[37]
    - Control of environmental allergens and cigarette smoke
  - Tertiary prevention aims at preventing irreversible damage to the inflamed organ, maximizing the remaining capabilities and functions of the organ.

2.3 | Third-level management of AR

Following second-line treatment, uncontrolled patients are invited to attend outpatient clinics for evaluation and advise regarding long-term therapeutic strategy. At this stage, the majority of AR patients with uncontrolled disease are seeking specialist advice. At specialist level, a treatment plan should ideally be proposed according to the needs of the patient, the achieved level of control, the availability of medication and the long-term ambition.

All four key principles of PM should be implemented during the follow-up consultation for AR at specialist level (Figure 2):

- *Prediction of success* of any step-down or step-up approach, with information on the expected benefits and risks of adverse events of long-term treatment
- *Participation of the patient* in the therapeutic plan, with clear information on the goals and practical implications of different therapeutic strategies in the short and long term
- *Prevention of disease progression* with clear statements on the different approaches for suppression of inflammation versus strategies for secondary (and tertiary) prevention of asthma. In occupational rhinitis, measures to prevent chronicity and development of asthma should be recommended, despite the major impact of the implementation. In AR, the sensitization pattern should guide the strategy for prevention of asthma, including the option of AIT.
- *Personalized care* with a treatment plan proposed on the base of the major or most bothersome symptom(s), the comorbidities, the endotype (type 2 inflammation, mixed inflammation or neurogenic inflammation and barrier impairment) and the patients' preferences, should be envisaged

2.4 | Integrated care pathways (ICPs)

A large number of AR patients do not consult physicians because they think AR symptoms are normal and/or trivial whereas AR impacts social life, school and work productivity.[13] Many AR patients use OTC drugs[16] and only a fraction have a medical consultation. The vast majority of patients visiting GPs or specialists have moderate/severe rhinitis.[38-42] Integrated care pathways differ from practice guidelines as they are utilized by a multidisciplinary team and have a focus on the quality and coordination of care, thus corresponding ideally to the requests of PM implementation at the point of care.[43] An ICP is intended to act as a guide to holistic disease management in a stepwise and feedback manner. AIRWAYS ICPs have proposed a multisectoral care pathway for AR (Figure 3 from[35]).

3 | GRADUAL IMPLEMENTATION OF THE FOUR PRINCIPLES OF PRECISION MEDICINE IN CRS

3.1 | First-level management of CRS

Chronic rhinosinusitis diagnosis is based on the presence of two or more sino-nasal symptoms and either CT scan for nonotorhinolaryngologists, supplemented by allergy tests in case of suspicion of concomitant allergy, and/or nasal endoscopy by otorhinolaryngologists for phenotyping into CRS with and without nasal polyps (CRSwNP and CRSsNP).

At the time of the first diagnosis of CRS in general or specialist practice, a therapeutic plan is elaborated taking into account the major presenting symptoms, the severity and impact of symptoms and comorbidities like asthma or chronic obstructive pulmonary disease (COPD) (Figure 4).[44,45] First-line treatment can be considered by every clinician taking care of patients with CRS.

At present, it seems clear that the following two key parameters of PM can easily be implemented at the time of elaboration of a first therapeutic plan (Figure 5):

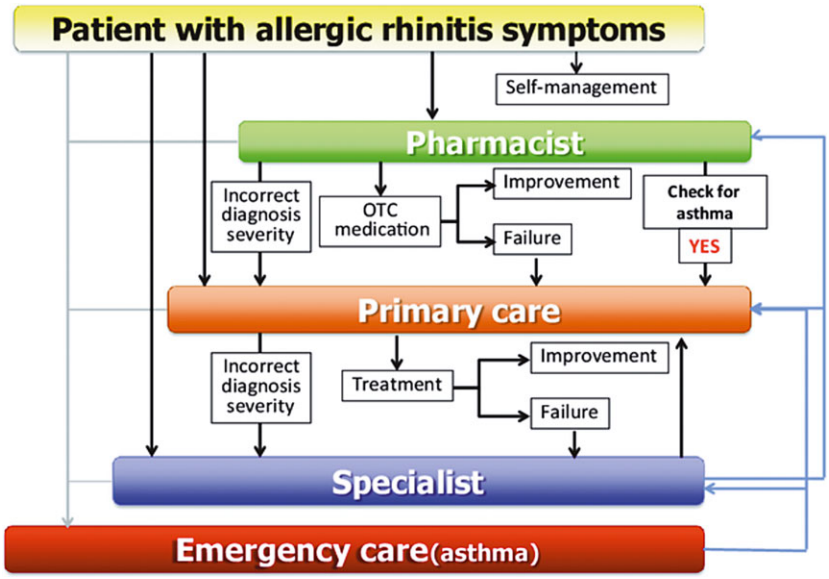

FIGURE 3 Multisectoral care pathway for allergic rhinitis (from Bousquet et al.[35]). OTC, over-the-counter

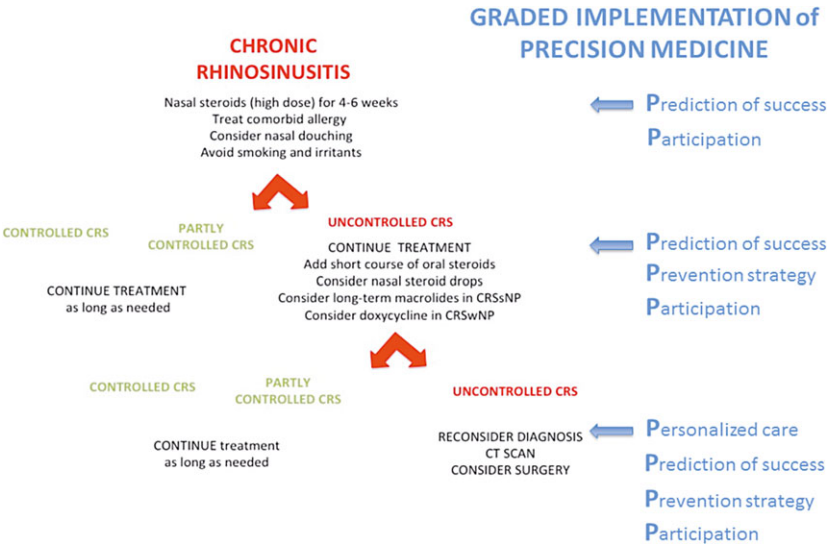

FIGURE 4 Graded implementation of precision medicine in chronic rhinosinusitis (adapted from Hellings et al.[11]). CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP:,chronic rhinosinusitis without nasal polyps

- *Prediction of success of treatment:* Physicians treating patients with CRS should be aware of the different therapeutic modalities for CRS, involving nasal steroids, nasal douching, avoidance of exposure to cigarette smoke and (professional) irritants and treatment of allergy in case of relevant sensitization and adapt to patient profile (EPOS), preferences and needs, taking into account the availability and accessibility to the recommended treatment choice. Therefore, the following information on prediction of success of treatment should be communicated to CRS patients:
  - Information on the expected onset of action and benefit of treatment of different treatment options, both on the symptom severity and on general functioning and quality of life
  - Information on the shortcomings, safety and potential adverse events of different treatment options and approaches
  - Information on the impact of treatment of CRS on the comorbidities, like asthma or COPD
  - Impact of exposure to irritants and allergens
- *Participation of the patient:* Given the proven efficacy of different options for treatment of CRS, patients are empowered as active partners in the elaboration of the following strategic choices for first-line treatment for CRS:
  - Choice of combined nasal corticosteroid treatment with nasal douching, or monotherapy
  - Choice of concomitant treatment of comorbid allergy, asthma or COPD

Also in CRS patients, education is a crucial step in the process of patient participation.

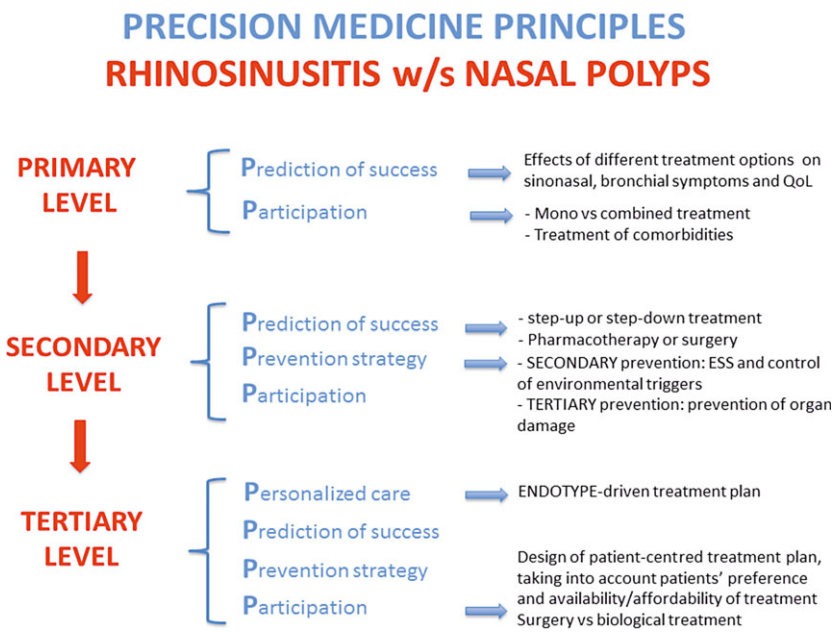

FIGURE 5 Precision medicine implementation in chronic rhinosinusitis. ESS, endoscopic sinus surgery; Qol, quality of life

After having elaborated a treatment strategy with the CRS patient, it is recommended to evaluate the degree of symptom control after a time interval of four weeks for patients with severe disease and three months for patients with mild-moderate disease.

Symptom control in CRS can be evaluated preferably by the application of the EPOS criteria for control. It is estimated that up to 50% of patients with CRS still remain symptomatic, with partially controlled or uncontrolled CRS. The latter population is seen at specialist level, for fine-tuning the diagnosis and designing an optimal therapeutic plan.

3.2 | Second-level management of CRS

Following the initiation of first-line treatment, uncontrolled CRS patients are invited for evaluation of the achieved level of symptom control and fine-tuning of the treatment strategy. Besides taking into account the achieved level of control by first-line treatment, a treatment strategy is elaborated according to the nasal endoscopic findings, the needs and expectations of the patient, the experienced efficacy and/or adverse events of the medication used, the availability of medication and the long-term goal of maintaining or achieving disease control and/or secondary or tertiary prevention of disease.

Therefore, the following key principles of PM can be implemented during the follow-up consultation for CRS (Figure 5):

- *Prediction of success* of any step-down or step-up approach, with information of the patient on the expected benefits and risks of the chosen approach
- *Participation of the patient* in the therapeutic plan, with clear explanation of the different treatment options for CRSwNP and CRSsNP, including (long term) oral antibiotics and oral corticosteroids
- *Prevention of disease progression* with clear statements on the different approaches for suppression of inflammation vs prevention of disease progression.
    - Secondary prevention in CRS aims to prevent the onset of asthma in those CRS patients who have not developed asthma symptoms or signs yet. Evidence-based therapeutic interventions for the secondary prevention of asthma fall into two categories:
        - Endoscopic sinus surgery (ESS): Recent evidence suggests that ESS may be associated with a reduced likelihood of developing asthma.[46,47]
        - Control of exposure to environmental allergens and cigarette smoke is considered important in preventing the disease progression. Retrospective data have shown the impact of occupational exposure to low molecular weight irritants on the success of ESS.[48,49]
    - Tertiary prevention aims to prevent irreversible damage to the inflamed organ, maximizing the remaining capabilities and functions of the organ. At this moment, tertiary prevention in CRS has not been studied.

3.3 | Third-level management of CRS

Following second-line treatment, uncontrolled patients are evaluated for advices regarding long-term therapeutic strategy, including the position of ESS.[29] At this stage, the majority of CRS patients with uncontrolled disease are seeking specialist advice. Specialists are supposed to fine-tune and reconsider the diagnosis in case of uncontrolled disease despite recommended treatment. At specialist level, a treatment plan should ideally be proposed according to the needs of the patient, the previously achieved level of control, the availability of medication and the long-term goal.

All four key principles of PM should be implemented during the follow-up consultation for CRS at specialist level (Figure 5):

- *Prediction of success* of medical versus surgical treatment, with information of CRS patients on the expected benefits of each

approach on the short and long term, and the risks or adverse events of both approaches. ESS is successful for most disease parameters in CRS, including asthma control, but persistent inflammation and need for postoperative medical care need to be discussed with the patient.[50] Also the balance between repetitive surgery, especially in patients with CRSwNP, and the side-effect of intensified medical treatment should be discussed.[51]

- *Participation of the patient* in the therapeutic plan, with clear information on the goals and practical implications of different therapeutic strategies on the short and long term, including postoperative care, importance of compliance to treatment regimes and avoidance of irritants.
- *Prevention of disease progression* with clear approaches for suppression of inflammation versus strategies for secondary prevention of asthma.
- *Personalized care* with an endotype-driven treatment plan, including biological treatment for CRSwNP, based on nasal inflammatory patterns.[52] Indeed, recent evidence highlights the benefit of biological treatment in CRSwNP patients, with superiority over oral corticosteroid therapy.[53-55] Easy-to-apply biomarkers are now needed to identify those patients who might benefit from biological treatment.

4 | CONCLUSIONS

PM represents the way forward for improved care in patients with chronic upper airway inflammation, and for prevention of asthma in patients with rhinitis and rhinosinusitis. Despite the perception of being associated with high cost of molecular analyses and biological treatment, most principles of PM can already be implemented in first- and secondary-level management without major costs. Given the diverse nature of uncontrolled disease, even implementing three of four principles of PM in routine care may lead to an increased degree of patient satisfaction, control of disease and prevention of asthma. AR patients may benefit from full control of disease with prevention of asthma, by the combination of regular pharmacotherapy and AIT. It is important to recognize that AR may be an optimal model to identify molecular causes for variable treatment response: AR is common, has a well-defined and accessible phenotype and often known external triggers (allergens). The disease process can be mimicked in vitro and in vivo to define novel biomarkers and drug targets for PM. Despite the emerging evidence of biologicals being the future of CRSwNP care, the long-term benefits still need to be confirmed. In addition, future studies are needed to confirm the benefit of the proposed care strategy for AR and CRS on socio-economic level as well as on the level of patient satisfaction and control of disease.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest related to this work.

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